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(54) Title: PHARMACEUTICAL FORMULATIONS WITH IMPROVED BIOAVAILABILITY

(57) Abstract: In accordance with the present invention there is provided a pharmaceutical formulation for modified release of an active ingredient in the gastrointestinal tract comprising a plurality of irregularly shaped cores and wherein an active ingredient.

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Pharmaceutical Formulations with Improved Bioavailability**FIELD OF THE INVENTION**

[01] The present invention relates to sustained release pharmaceutical formulations with improved absorption and bioavailability of pharmaceutical active agents with limited or region specific absorption and/or pH dependent absorption profile after oral administration.

BACKGROUND OF THE INVENTION

[02] The absorption process of pharmacologically active compounds after oral administration depends, to a large extent, on the physicochemical properties of the active ingredient. This dependency makes certain regions of the intestinal tract more amenable to a given drug's absorption. Optimal absorption is then achieved when the residence time of the drug, at its specific region of absorption, is prolonged. When drug transit through the absorptive region is short, sub-optimal plasma levels are achieved resulting in a short duration of action. Moreover, it makes it difficult to create sustained release formulations for oral administration.

[03] Consequently, the short residence time in the small intestine poses a considerable problem to those skilled in the art interested in developing sustained absorption medicinal products intended for oral administration. The medicinal product administered orally is, in effect, subject to the natural transit of the gastrointestinal tract, thereby limiting its residence time.

[04] US Patent No. 6,267,990 describes controlled release pharmaceutical preparations comprising an ACE inhibitor as active ingredient. This patent relates to the use of spherical pellets with two delayed release populations within the delivery system. The system is not retentive, and pH specific coating is the only means by which region specific release is brought about. With such systems, if the pH dependent polymer coating is dissolved too rapidly or too slowly, suboptimal absorption profiles are resulted.

[05] US Patent No. 5,158,777 generally describes a captopril oral delivery system containing spherical beads coated with pH dependent polymer for delayed/enteric release.

[06] US Patents 5,912,013 and 5,326,570, describe dosage forms containing carbamazepine, some of which have been subsequently found to be of irregular shaped particles. However, these particles are not of a sustained release matrix formulation.

[07] It would therefore be advantageous to be able to deliver a drug with a region of absorption limited to the small intestine, particularly the upper half of the small intestine, and increase the drug's residence at this site, which is the preferred location for systemic absorption for a number of active pharmaceutical agents, and be able to make such a dosage form a sustained release matrix formulation.

SUMMARY OF THE INVENTION

[08] In accordance with the present invention, there is provided a pharmaceutical formulation for sustained release of an active ingredient in the gastrointestinal tract, comprising a plurality of irregularly shaped cores and wherein the active ingredient is chosen from those agents that have region of absorption limitations, for instance drugs with windows of absorption of less than six hours after ingestion. As examples thereof are certain drugs in the categories of cardiovascular agents, ACE inhibitors, antimicrobials, proton pump inhibitors, antivirals, cancer chemotherapeutic agents, vitamin B₆ derivatives, benzodiazepines, analgesics, anticholinergics, anti-ADHD agents, antiepileptics, and phosphodiesterase III inhibitors, although the present invention is not limited to this list.

[09] The present invention provides for such a formulation in the form of a matrix-type sustained release composition. Such a dosage form provides for the sustained release administration of such an active ingredient as mentioned above, which will thereby allow a patient to take fewer dosages during the course of treatment. Ideally, in some situations, the dosage forms of the present invention will allow for a once-a-day dosing regimen.

[010] The present invention also provides a method of making the irregular cores of the present invention, as well as dosage forms containing such cores.

[011] In another aspect, there is provided a method for the treatment of a disease comprising administering a formulation in accordance with the present invention to a patient in need of such treatment.

[012] In a further aspect there is provided the use of a formulation in accordance with the present invention for the preparation of a medicament for the treatment of a disease.

Brief description of the drawings

[013] Various other features and attendant advantages of the present invention will be more fully appreciated as the same becomes better understood when considered in conjunction with the accompanying drawings wherein:

[014] Figure 1 shows the dissolution profile of an anagrelide extended-release capsule according to Example 2 (PD0073-124A).

[015] Figure 2 shows the dissolution profile of an anagrelide extended-release capsule according to Example 2 (PD0073-124B).

[016] Figures 3A and B represent photomicrograph of cores made according to the invention (A) compared to sugar spheres (B). Microscope Settings: 25X Lens with 1,000X magnification.

[017] Figure 4 shows the mean dissolution (n=6) profile for trospium chloride from roller compacted granules. Dissolution medium: phosphate buffer, pH 6.8. USP apparatus II, 50 RPM.

DETAILED DESCRIPTION OF THE INVENTION

[018] In one embodiment, compositions and their preparation and use in accordance with the present invention comprise those wherein the following embodiments are present, either independently or in combination.

[019] The current invention provides for irregularly shaped matrix cores containing at least one pharmaceutical active ingredient along with appropriate inactive excipients to yield robust cores. By "irregular" shape is meant, generally, non-spherical.

[020] In order to accommodate for optimal absorption, the prior art has focused on attaining beadlets that are spherical, which will enhance surface area as well as provide particles that are more easily processed, for instance more easily coated. However, such systems fall short of increased retention at the site of absorption due to their geometric configuration. By their nature, sphere-like structures have an increased tendency to "roll down" a given path with the least amount of resistance secondary to friction. Therefore, a non-spherical, irregularly shaped core system was developed which results in increased transit time as compared to a spherical system.

[021] Roundness, or sphericity, is described as the degree of abrasion of a clastic particle as shown by the sharpness of its edges and corners, expressed by Wadell (1932) as the ratio of the average radius of curvature of the several edges or corners of the particle to the radius of curvature of the maximum inscribed sphere (or to one-half the nominal diameter of the particle.) Bates, R. L. and Jackson, J. A., 1980, Glossary of Geology, 2nd Edition. Falls Church, Virginia, American Geological Institute, p. 546. Krumbein et al. describes this visually in Krumbein, W. C. and L. L. Sloss

(1951) Stratigraphy and Sedimentation. 2nd. Ed. W. H. Freeman and Company. London.

[022] The majority of the distribution of cores (the production of particles typically results in a bell-shaped distribution of size and shape) of the present invention is not spherical (Wadell sphericity of 1), and preferably has a Wadell sphericity value of 0.7 or less, or a corresponding roundness value of less than 0.40 (subrounded to very angular, see Bates and Jackson, *supra*). More preferably, the majority of the core distribution is between a roundness value of 0.0 and 0.25 (subangular to angular).

[023] Without being bound to any particular theory, it is believed that the cores of the present invention provide for increased retention time based on their geometric configuration; due to their non-spherical and irregular morphologies, they are more apt to get "caught up" in the crevices within the gastrointestinal tract's convoluted morphology of the epithelial barrier.

[024] The increased transit time is also dependent on the force exerted by the gastric or intestinal fluid on the particle as the fluid moves through the GI tract. The force is a result of the relative motion between the cores and the surrounding GI fluid. This can be expressed in mathematical terms in accordance with the following equation.

$$F = C A \rho \mu^2 / 2 g c$$

where C is the coefficient of drag, A_p is the projected particle area in the direction of motion, ρ is the density of the GI fluid, μ is the relative velocity between the particle and the GI fluid and g_c is the dimensional constant.

[025] The cores of the present invention have a reduced A_p due to their non-spherical, highly irregular shape, thus reducing the value of F leading to slower transit time. The shape factor is a dimensionless number that has been used to mathematically compare the area of an irregularly shaped particle to the area of a sphere of an equivalent volume as the volume of the irregularly shaped particle. The shape factor of a sphere is 1.0 while the shape factor of the irregularly shaped cores is less than 1.0. The more irregularly shaped the particle the lower the shape factor.

[026] In one aspect of the invention, the majority of the irregular shaped cores have a particle size of about $50\mu\text{m}$ to about $3000\mu\text{m}$. Preferably, the majority of the irregular shaped cores have a particle size of about $100\mu\text{m}$ to about $2000\mu\text{m}$. Most preferably, the majority of the irregular shaped cores have a particle size of about $100\mu\text{m}$ to about $1000\mu\text{m}$. The upper limits are desirable to ensure the particles are not too big to hamper further processing, such as filling into capsules. The lower limits are necessary to ensure that the particles contain all of the components required for the matrix character and the drug or drugs. Control of the size of the particles is within the knowledge and skill of one in the art. For instance, with roller compaction, two different screen sizes are utilized to

obtain certain size ranges. For example, using mesh 18 and mesh 35 will yield cores of between about 125 and about 800 microns.

[027] The drug (active ingredient) is present within the microparticulates from about 0.1% (w/w) to 99.0% (w/w), preferably from about 1.0% (w/w) to about 80% (w/w), depending on the drug and dosage.

[028] The pharmaceutically active ingredient is chosen from incompletely absorbed (limited oral bioavailability) pharmaceutical agents, which include *inter alia* certain ACE inhibitors, antimicrobials, benzodiazepines, anticholinergics, muscarinic receptor antagonists, adenosine A₁ agonists, and phosphodiesterase inhibitors. The incomplete oral absorption of the active ingredient is due to region specificity for the drug's absorption within the GI tract. The region specificity may be due to the pH of the microenvironment and/or the region's inherent permeability to the active ingredient.

[029] One aspect of the present invention relates to the use of the cores of the present invention for sustained delivery of ACE inhibitors. ACE inhibitors are compounds which inhibit the conversion of angiotensin I to the vasoconstrictor compound angiotensin II as well as the breakdown of the active vasodilator, bradykinin. These activities result in a reduction of peripheral arterial resistance and thus a reduction of blood pressure. ACE inhibitors are being used as effective therapy for hypertension as well as congestive heart failure. Examples of ACE inhibitors that would benefit from being in the dosage forms of the present invention are fasidotril, enalaprilat, or ramipril, or mixtures thereof, which are incompletely absorbed due to the region's inherent permeability to the drug.

[030] Among phosphodiesterase III inhibitors, anagrelide is incompletely absorbed due to a combination of pH and solubility of the active ingredient.

[031] Examples of antimicrobials with region specificity include doxycycline and tetracycline.

[032] An example of an anticholinergic with absorption limitations is trospium chloride. In fact, quaternary ammonium compounds generally have inherently low absorption in the GI tract and as such only certain specific regions (upper duodenum) are optimal for absorption. Thus, other quaternary ammonium compounds would benefit from being composed in accordance with the present invention as well.

[033] Among proton pump inhibitors, all prazole derivatives are region specific due to the pH of the microenvironment. These drugs degrade at low pH (<5).

[034] An example of a muscarinic receptor antagonist is trospium chloride.

[035] Among cancer chemotherapeutic agents are chlorambucil, carboplatin, derivatives of busulfan, doxorubicin, etoposide, and topotecan (TPT), which are incompletely absorbed due to permeability and pH issues.

[036] Among anti-epileptics is particularly gabapentin, which is incompletely absorbed.

[037] Among analgesics that have region specificity are codeine and morphine.

[038] Among benzodiazepines with region specificity are clonazepam, midazolam and triazolam.

[039] Among cardiovascular agents is verapamil.

[040] It will be appreciated by those skilled in the art that the active ingredients can be used in the form of pharmaceutically acceptable salts or esters or derivatives and in the case of chirally active ingredients, one can use both optical isomers, geometric isomers and mixtures thereof, including racemic mixtures. Moreover, the above-listed examples do not comprise a comprehensive list and other drugs with region of absorption concerns are contemplated as useful in the present invention.

[041] The majority (i.e., more than 50%) of the cores of the present invention must have irregular, non-spherical shapes and as such the preparation of the cores is done using technologies capable of such geometric irregularity. One means for the preparation of the cores is through roller compaction of a dry blend. For example, the cores of the present invention can be prepared by screening each component through a mesh sieve and dry blending the mixture in a V-blender. The blended powders are then processed through a roller compactor, where the blends are compacted and dry granulated to form cores of non-spherical shapes. The cores are typically then screened through appropriate meshes such as 18 and 40 mesh sieves.

[042] Another means to obtain cores of the present invention that have irregular and non-spherical/angular morphology is by high shear granulation or roto-granulation (for wet granulation processes). Yet another means for obtaining the cores is by milling (hammer milling, roller milling, etc.) processes that reduce particle size of substrate to the ranges specified herein.

[043] The most preferred approach for manufacture of such cores is the roller compaction technology, through which, unexpectedly, mostly non-spherical cores are obtained according to the present invention.

[044] By "sustained release" is meant a formulation that temporally releases the active ingredient to tissues, or releases drug temporally to be absorbed through the GI tract to the blood stream, thus to the targeted tissue.

[045] The cores are formed into a matrix composition to attain their sustained released nature. Matrix devices can be composed of insoluble plastics, hydrophilic polymers, or hydrophobic or fatty compounds.

[046] Making a matrix composition involves, for example, adding a powdered wax at 5-30% of the total formulation weight, such as hydrogenated castor oil, glyceryl palmitostearate, glyceryl behenate, Gelucire, PEG 8000 or any other known non-swellable matrix forming agent. The wax may be granulated with any component or combination of components of the formulation with a 0-20% PVP K25 or PEG 8000 or other binder solution, and after subjecting to a procedure that favors non-spheroidal particles, the particles are then added to any remainder of the formulation (for tableting or encapsulating, for instance) using known methods.

[047] The cores of the present invention may further be coated with one or more coating agents, such as enteric coatings. Such coating agents are not generally soluble in the stomach environment, are slowly soluble in the GI tract, or are soluble at various pHs.

[048] Hydrophobic or fatty components useful for matrix formulations include, for example, ethyl cellulose, glyceryl monostearate, mixtures of glyceryl monostearate and glyceryl monopalmitate, glyceryl monooleate, a mixture of mono-, di and triglycerides, glyceryl monolaurate, paraffin, white wax, glyceryl dibehenate, long chain carboxylic acids, long chain carboxylic acid esters or long chain carboxylic acid alcohols.

[049] For the preparation of matrix cores one can also include one or more hydrophilic polymers in the formulation. Hydrophilic polymers include, but are not limited to, swellable hydrophilic polymers and non-swellable hydrophilic polymers.

[050] Hydrophilic swellable polymers include, for example, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polymethacrylic acid copolymers, polycarbopols, or polyethylene oxides.

[051] Non-swellable hydrophilic polymers include, for example, polyethylene glycol, ethylcellulose (e.g., Ethocel®), cellulose acetate, cellulose ester butyrate, cellulose acetate proprionate, cellulose acetate phthalate, methacrylic acid and ammoniomethacrylic acid polymers, such as all the Eudragit polymers, Eudragit RS, Eudragit RL, and enteric polymers such as Eudragit L30D-55 and Eudragit FS30D.

[052] Plastics used in matrix tablets include, for instance, methyl acrylate-methyl methacrylate, polyvinyl chloride and polyethylene.

[053] Enteric coating agents include, for instance, polymers that are substantially insoluble in the acidic environment of the stomach, but are predominantly soluble in intestinal fluids at specific pHs. The enteric materials are

non-toxic, pharmaceutically acceptable polymers, and include, for example, cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, natural resins such as zein, shellac and copal colophonium, and several commercially available enteric dispersion systems (e.g., Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, and Aquateric). The foregoing is a list of possible materials, but one of skill in the art would recognize that it is not comprehensive and that there are other enteric materials that would meet the objectives of the present invention of providing for a modified release profile.

[054] Alternatively, the coating can contain one or more polymers that are soluble at various, or different in the case of more than one, pHs. These sustained release coatings will allow for a release delayed until the pH of the environment is such that it will allow the coating to dissolve. Hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP) and Coateric will dissolve in buffers of pH 5.0 and higher. Eudragit L100-55, Eudragit L30D-55, Kollicoat

EMM30D, and Estacryl 30D will dissolve from pH5.5 to 6.5. Cellulose acetate phthalate (CAP) and Aquateric will dissolve in buffers above pH 6.2. Eudragit S100 and FS30D will dissolve around pH7.0-7.5. Roughly, the pH of the duodenum is about 5.5, the jejunum is about 6.5 and the distal ileum is about 7.5.

[055] The formulation of the present invention may further include other materials such as permeation/absorption/solubility enhancers or promoters, bulking agents, disintegrating agents, anti-adherants and glidants, lubricants, and binding agents.

[056] Permeation/absorption enhancers or promoters include but are not limited to cationic, anionic, and nonionic surfactants, medium chain glycerides, blends of mono- di-, and triglycerides, or vitamin E TPGS.

[057] Bulking agents include, but are not limited to, microcrystalline cellulose (e.g., Avicel®, FMC Corp., Emcocel®, Mendell Inc.), mannitol, xylitol, dicalcium phosphate (eg. Emcompress, Mendell Inc.) calcium sulfate (eg. Compactrol, Mendell Inc.) starches, lactose, sucrose (Dipac, Amstar, and Nutab, Ingredient Technology), dextrose (Emdex, Mendell, Inc.), sorbitol, cellulose powder (Elcema, Degussa, and Solka Floc, Mendell, Inc.) The bulking agent may be present in the composition in an amount of from about 1 wt. % to about 90 wt. %, preferably from about 10 wt. % to about 50 wt. %.

[058] Disintegrating agents that may be included in the composition include, but are not limited to, microcrystalline cellulose, starches, crospovidone (eg. Polyplasdone XL, International Specialty Products.), sodium starch glycolate (Explotab, Mendell Inc.), and crosscarmellose sodium (eg. Ac-Di-Sol, FMC Corp.).

The disintegrating agent may be present in the composition in an amount of from about 0.1 wt. % to about 30 wt %, preferably from about 1 wt. % to about 15 wt. %.

[059] Antiadherants and glidants which may be employed in the composition include, but are not limited to, talc, corn starch, silicon dioxide, sodium lauryl sulfate, and metallic stearates. The antiadherant or glidant may be present in the composition in an amount of from about 0.2 wt. % to about 15 wt. %, preferably from about 0.5 wt. % to about 5 wt. %.

[060] Lubricants which may be employed in the composition include, but are not limited to, magnesium stearate, calcium stearate, sodium stearate, stearic acid, sodium stearyl fumarate, hydrogenated cotton seed oil (sterotex), talc, and waxes, including but not limited to, beeswax, carnuba wax, cetyl alcohol, glyceryl stearate, glyceryl palmitate, glyceryl behenate, hydrogenated vegetable oils, and stearyl alcohol. The lubricant may be present in an amount of from about 0.05 wt. % to about 20 wt. %, preferably from about 0.5 wt. % to about 5 wt. %.

[061] Binding agents which may be employed include, but are not limited to, polyvinyl pyrrolidone, starch, methylcellulose, hydroxypropyl methylcellulose, carboxymethyl cellulose, sucrose solution, dextrose solution, acacia, tragacanth and locust bean gum. The binding agent may be present in the composition in an amount of from about 0.2 wt. % to about 10 wt. %, preferably from about 0.5 wt. % to about 5 wt. %.

[062] A protective coat (e.g., OPADRY® beige or white) also can be applied onto the cores or tablets to provide color or physical protection.

[063] As long as the presentation of the cores, as described in the present invention, in the gastrointestinal tract is in the form of non-spherical irregularly shaped particulates, the dosage form can be prepared as single or multi-layered, coated or uncoated, tablets or beads of a capsule.

[064] The compositions of the present invention may be made into a tablet by any tableting method, such as direct compression, wet or dry granulation, or fluid bed granulation. In the direct compression method, the resultant blends of the cores of the present invention and any other excipients are compressed into tablets on a rotary press using appropriate tooling. In compressing the cores of the invention into a tablet, it is important that the irregularity of the cores be mostly maintained by, for instance using a cushioning type of tablet filler such as microcrystalline cellulose and the like. It will be apparent to one skilled in the art that different agents can be added to the core mixture when preparing the tablet. For example, a disintegrant can be added to the mixture, which will allow the cores to be released in the GI tract. The compressed tablets and/or the cores may be coated, if desired.

[065] For powder forms, such as sachets, no further processing of the cores is necessary. For capsules, which are the preferred dosage forms herein, the cores, which are coated or not, are encapsulated into hard or soft capsules. For any of the dosage forms, there may be mixtures of the cores of the present invention as well as conventional, round cores in order to obtain different, such as pulsatile, release profiles. For example, a tablet or capsule may contain multiple

cores or particulates, the concept of which is disclosed, for instance in US Patent No. 6,322,819, which is hereby incorporated herein by reference.

[066] The compositions of the present invention may be employed to treat a variety of diseases or disorders. For example, when the pharmaceutically active agent is anagrelide hydrochloride, the composition may be employed in treating a variety of blood disorders, including, but not limited to, myeloproliferative blood disorders or MBDs, such as, for example, essential thrombocythemia, or ET, chronic myelogenous leukemia, or CML, polycythemia vera, or PV, and agnogenic myeloid metaplasia, or AMM. The composition including anagrelide HCl may be administered to an animal, such as a mammal, including human and non-human primates, in an amount effective to treat such disorders.

[067] Trospium chloride is an antimuscarinic drug used for the treatment of detrusor instability or detrusor hyperreflexia, with the symptoms of urinary frequency, urgency, and incontinence, as well as for the control of spasms in genitourinary tract disorders. It works to prevent smooth muscle contraction such as that found in the bladder by blocking the effects of acetylcholine. Dosage is typically 20 mg twice daily. Fusgen et al., Hauri D. Trospium chloride: an effective option for medical treatment of bladder overactivity. *Int J Clin Pharmacol Ther* 2000;38:223-234. By use of the present invention, a once a day formulation is attainable. For such a once-a-day dosage, anywhere from about 20 mg. to about 120 mg. of trospium chloride is used, depending on the particular composition of the irregular cores. Preferable is a dosage of about 40 to about 120 mg., and most preferred is a 40 mg. dosage form.

[068] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

[069] It will be appreciated that the amount of a compound of the invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition for which treatment is required and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general however a suitable dose will be in the range of from about 0.0001 to about 50 mg/kg of body weight per day, preferably in the range of 0.01 to 40 mg/kg/day, most preferably in the range of 0.015 to 20 mg/kg/day.

[070] The desired dose may conveniently be presented in a single dose or as divided dose administered at appropriate intervals, for example as two, three, four or more doses per day.

[071] The following examples are provided to illustrate various embodiments of the present invention and shall not be considered as limiting in scope.

Examples

Example 1

[072] Typical cores compositions are shown in Table 1. Both formulations contain an active pharmaceutical agent. Formulations A and B are prepared by screening each component through a mesh 18 sieve and blending the mixture in a V-blender for 10 minutes. The respective blended powders are then processed through a roller compactor, where the blends are compacted and dry granulated to form cores. The cores are screened through mesh 18 and mesh 40 sieves and the irregular shaped cores in between is collected and encapsulated into size 3 hard gelatin capsules using an encapsulator.

Table 1. Composition of Core Formulations

Ingredients	Formulation A		Formulation B	
	1	2	1	2
Active Pharmaceutical Agent	10	12	10	10
Ludipress	32	38	30	30
Prosolv HD90	28	34	14	14
Methocel E5	12.50	15	10	10
Methocel K4M	----	----	35	35
Pruv	0.83	1	1	1

1 = composition in mg per capsule

2 = composition in % weight

Note:

Ludipress is a trade name for a blend of lactose, polyvinyl pyrrolidone, and crosslinked polyvinyl pyrrolidone and marketed by BASF Corporation.

Prosolv HD90 is a trade name for silicified microcrystalline cellulose and marketed by Penwest Corp.

Methocel E5 is a trade name for hydroxypropyl methylcellulose and marketed by the Dow Chemical Company.

Methocel K4M is a trade name for hydroxypropyl methylcellulose and marketed by Dow Chemical Company.

Pruv is a trade name for sodium stearyl fumarate and is marketed by Penwest Corp.

Example 2

[073] Anagrelide compositions are shown in Table 2. Both formulations contain anagrelide HCl as the active pharmaceutical agent. Formulations PD0073-124A and PD0073-124B were prepared by screening each component through a mesh 18 sieve and blending the mixture in a V-blender for 10 minutes. The respective blended powders were then processed through a roller compactor, where the blends were compacted and dry granulated to form irregular cores. The cores were screened through mesh 18 and mesh 40 sieves and the material in between was collected and encapsulated into size 3 hard gelatin capsules using an encapsulator.

Table 2. Composition of Core Formulations of Anagrelide HCl

Ingredients	PD0073-124A		PD0073-124B	
	1	2	1	2
Anagrelide HCl	1.22	0.61	1.22	0.61
Polyox WSR 301	80	40	---	---
Avicel pH101	30	15	10	5
Fujicalin	30	15	---	---
Eudragit S100	30	15	30	15
Eudragit L100	---	---	20	10
Fumaric acid	10	5	---	---
Ethocel	---	---	80	40
Eudragit RS	---	---	20	10
Compritrol	18.78	9.39	38.78	19.39

1 = composition in mg per capsule

2 = composition in % weight

Note: Polyox WSR 301 is a trade name for poly(ethylene oxide) and is marketed by Union Carbide. Avicel pH 101 is a trade name for microcrystalline cellulose and is marketed by FMC Biopolymer. Fujicalin is a trade name for dibasic calcium

phosphate and is marketed by Fuji Chemical Industry Co., Ltd. Eudragit S100 is a trade name for poly(methacrylic acid-co-ethyl acrylate) and is marketed by Rohm GmbH. Eudragit L100 is a trade name for poly(methacrylic acid-co-ethyl acrylate) and is marketed by Rohm GmbH. Ethocel is a trade name for ethylcellulose and is marketed by the Dow Chemical Company. Eudragit RS is a trade name for poly(methacrylic acid-co-ethyl acrylate) and is marketed by Rohm GmbH. Compritol is a trade name for glyceryl behenate and is marketed by Gattefosse.

[074] Anagrelide irregular cores formulations were tested for drug release as a function of time in a USP dissolution apparatus using acid media as well as neutral (pH 6.8) media. The results are shown in Figures 1 and 2. Both formulations were able to sustain the release of anagrelide over a prolonged period of time.

Example 3

[075] To depict the irregular and non-spherical morphology of the cores, the subject of this invention, cores were developed and photographed. The cores were developed according to the procedure outlined in Example 1. Figure 3A shows cores in accordance to the current invention and Figure 3B shows 25-35 mesh sugar spheres. The cores of Figure 3A can be rated as 0.1 to 0.2 on the Krumbein visual scale.

Example 4 - Roller compacted trospium preparation for extended release

[076] The composition is shown in Table 3. Drug and excipients were screened through an 18-mesh sieve and mixed in a V-blender for 5 minutes. The blend was then roller compacted. The roller compactor processing parameters are: roller speed = 8 rpm; feed screw speed = 25 rpm; granulator speed = 80 rpm;

roller pressure = 100 bar; and top/bottom screens are 1.25mm/0.63mm. Granules obtained were screened and those retained between 20- and 50-mesh sieves were collected. Granules were encapsulated in size 0 white opaque coni-snap capsules and analysed for dissolution. Figure 4 shows the mean dissolution profile for PD0150-182E.

Table 3

Ingredients	% Composition
Trospium Chloride	20
Prosolv HD90	40
Compritol 888ATO	20
Klucel EXF	10
Kollidon K30	10

Note: Klucel EXF is hydroxypropylcellulose, available from Hercules, Inc., Delaware.

Kollidon K30 is povidone, manufactured by BASF.

Example 5

[077] The following formulations were blended as described in the previous examples, and roller compacted with the following parameters: top screen: 1.25 mm, bottom screen: 0.8 mm; feed screw speed = 19 rpm; roller speed = 8 rpm; granulator speed = 70 rpm; and roller pressure = 150 bar.

Ingredient	%w/w
Topiramate	40
Avicel 301	39
HPMC K15 CR	20
Magnesium Stearate	1

Ingredient	%w/w
Topiramate	40

Compritol 888ATO	30
Prosolv HD90	24
HPMC K15 CR	5

Example 6

[078] The following formulations were blended as described in the previous examples, and roller compacted with the following parameters: top screen: 1.25 mm, bottom screen: 0.63 mm; feed screw speed = 25 rpm; roller speed = 8 rpm; granulator speed = 80 rpm; and roller pressure = 100 bar.

Ingredient	%w/w
Trospium Chloride	20
Klucel EF	10
Prosolv HD90	20
Kollidon K30	10
Compritol ATO888	20
Methocel K100M	20

Ingredient	%w/w
Trospium Chloride	20
Klucel EXF	10
Prosolv HD90	40
Kollidon K30	10
Compritol ATO888	20

Example 7

[079] SLI460 is an adenosine A₁ agonist. All ingredients in each of the tables below were sieved through a size 30 mesh screen. Formulation was PK blended without API (active pharmaceutical ingredient) for 5 minutes without intensifier bar. Upon adding API to blend, formulation was blended 3 minutes with intensifier bar, then additional 2 minutes without intensifier bar. Formulation was

then passed through the roller compactor, collecting microparticulates between sizes 18-35 mesh sieves. The remaining particles were passed through the roller compactor and collected in the same manner for an additional 2 passes.

[080] Blends were roller compacted with the following parameters: top screen: 2.5 mm, bottom screen: 1.0 mm; feed screw speed = 25 rpm; roller speed = 8 rpm; granulator speed = 70 rpm; and roller pressure = 100 bar.

Ingredient	%w/w
SLI460	1.5
Fumaric Acid	5
Methocel K15 CR	13.5
Compritol 888ATO	15
Ludipress	40
Polyox WSR	15
Avicel 101	10

Ingredient	%w/w
SLI460	1.5
Fumaric Acid	5
Methocel K15 CR	29
Compritol 888ATO	15
Ludipress	18.5
Polyox WSR	30
Avicel 101	1

Ingredient	%w/w
SLI460	1.5
Fumaric Acid	0.5
Methocel K15 CR	30
Compritol 888ATO	25
Eudragit RSPO	41.5
Avicel 101	1.5

[081] The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention. From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1. A pharmaceutical composition for delivery of an active pharmaceutical agent that has a region of absorption specificity that limits the bioavailability of the agent, which comprises a plurality of substantially non-spherical cores containing said active agent in a matrix formulation.
2. The composition of claim 1, wherein the majority of the non-spherical cores have a sphericity according to Wadell of less than 1.
3. The composition of claim 2, wherein the majority of the non-spherical cores have a sphericity according to Wadell of less than 0.7.
4. The composition of claim 1, wherein the majority of the non-spherical cores are subrounded to very angular.
5. The composition of claim 4, wherein the roundness value is 0.4 or less.
6. The composition of claim 1, wherein the cores are coated with at least one enteric or sustained release coating.
7. The composition of claim 1, wherein the cores are compressed in the form of a tablet.
8. The composition of claim 7, wherein the tablet is coated with at least one enteric or sustained release coating.
9. The composition of claim 1, wherein the cores are filled into a capsule.
10. The composition of claim 9, wherein the capsule contains coated and uncoated cores.

11. The composition of claim 9, wherein the capsule contains multiple forms of cores, which are present in such proportions as to obtain a pulsatile release profile of said agent.
12. The composition of claim 1, wherein the active agent is selected from ACE inhibitors, antimicrobials, benzodiazepines, anticholinergics, muscarinic receptor antagonists, adenosine A₁ agonists, and phosphodiesterase inhibitors.
13. The composition of claim 1, wherein the active agent is a quaternary ammonium compound.
14. The composition of claim 12, wherein the active agent is trospium or a salt thereof.
15. The composition of claim 14, wherein the active agent is trospium chloride.
16. The composition of claim 12, wherein the active agent is an adenosine A₁ agonist.
17. The composition of claim 8, wherein said enteric coating is one or more selected from cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid,

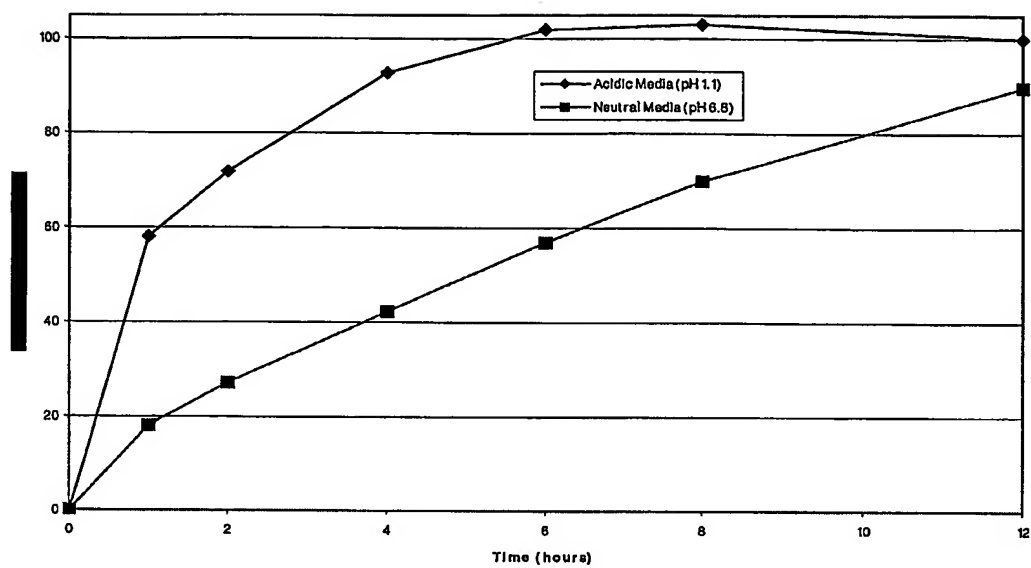
copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, zein, shellac, copal colophonium, Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, and Aquateric.

18. The composition of claim 8, wherein said sustained release coating is one or more selected from hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), Coateric, Eudragit L100-55, Eudragit L30D-55, Kollicoat EMM30D, Estacryl 30D, cellulose acetate phthalate (CAP), Aquateric, Eudragit S100, and Eudragit FS30D.
19. A process of preparing cores of pharmaceutically active agents, comprising mixing a pharmaceutically active agent that has a region of absorption specificity that limits the bioavailability of the agent with one or more matrix materials to thereby form a matrix core, and subjecting the resulting mixture to one of roller compaction, hammer milling or roller milling.
20. The process of claim 19, further comprising the step of compressing the cores produced thereby into a tablet.
21. The process of claim 20, further comprising coating said tablet with one or more enteric coatings.
22. The process of claim 19, wherein said matrix materials are selected from insoluble plastics, hydrophilic polymers or hydrophobic/fatty compounds.
23. The process of claim 22, wherein said hydrophobic/fatty compounds are one or more of ethyl cellulose, glyceryl monostearate, mixtures of glyceryl

monostearate and glyceryl monopalmitate, glyceryl monooleate, a mixture of mono-, di and triglycerides, glyceryl monolaurate, paraffin, white wax, glyceryl dibehenate, long chain carboxylic acids, long chain carboxylic acid esters and/or long chain carboxylic acid alcohols.

24. The process of claim 23, wherein said hydrophobic/fatty compounds are selected from hydrogenated castor oil, glyceryl palmitostearate, glyceryl behenate, Gelucire, and/or PEG 8000.
25. The process of claim 22, wherein said hydrophilic polymers are selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose, polymethacrylic acid copolymers, polycarbopols, polyethylene oxides, polyethylene glycol, ethylcellulose, cellulose acetate, cellulose ester butyrate, cellulose acetate proprionate, cellulose acetate phthalate, methacrylic acid, Eudragit RS, Eudragit RL, Eudragit L30D-55 and Eudragit FS30D.
26. The process of claim 25, wherein said hydrophilic polymer is hydroxypropyl methylcellulose.
27. The process of claim 22, wherein said insoluble plastic is selected from methyl acrylate-methyl methacrylate, polyvinyl chloride and polyethylene.
28. A method of treating a patient with a sustained release pharmaceutically active agent, comprising orally administering a pharmaceutical dosage form that comprises a plurality of substantially non-spherical cores containing said active agent in a matrix formulation.

29. The method of claim 28, wherein the majority of the non-spherical cores have a sphericity according to Wadell of less than 1.
30. The method of claim 29, wherein the majority of the non-spherical cores have a sphericity according to Wadell of less than 0.7.
31. The method of claim 28, wherein the majority of the non-spherical cores are subrounded to very angular.
32. The method of claim 31, wherein the roundness value is 0.4 or less.
33. The method of claim 28, wherein the cores are coated with at least one enteric or sustained release coating.
34. The method of claim 28, wherein said active agent is selected from ACE inhibitors, antimicrobials, benzodiazepines, anticholinergics, muscarinic receptor antagonists, adenosine A₁ agonists, and phosphodiesterase inhibitors.
35. The method of claim 28, wherein the active agent is a quaternary ammonium compound.
36. The method of claim 28, wherein the active agent is trospium or a salt thereof.
37. The method of claim 36, wherein the active agent is trospium chloride.
38. The method of claim 34, wherein the active agent is an adenosine A₁ agonist.

**Figure 1**

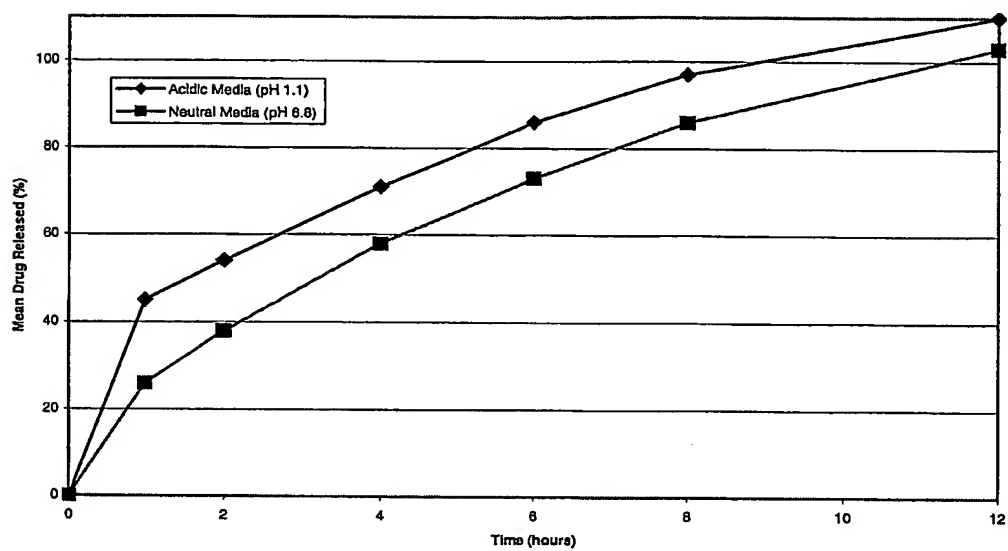
**Figure 2**

Figure 3(A)

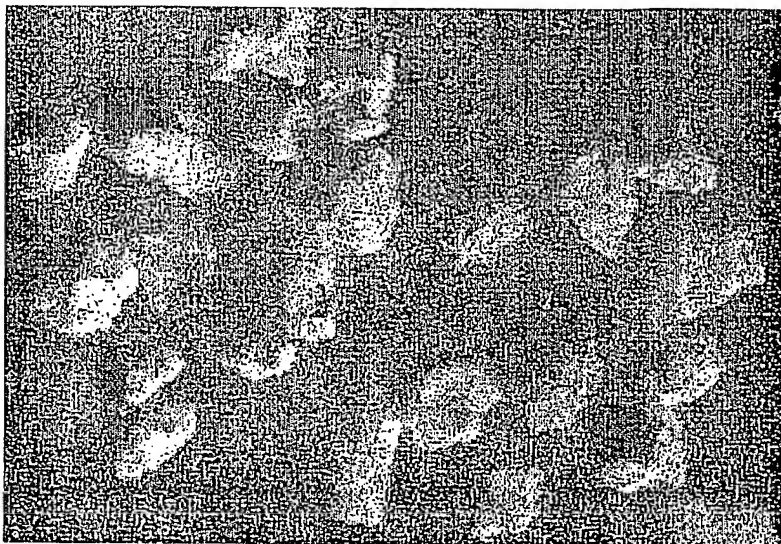
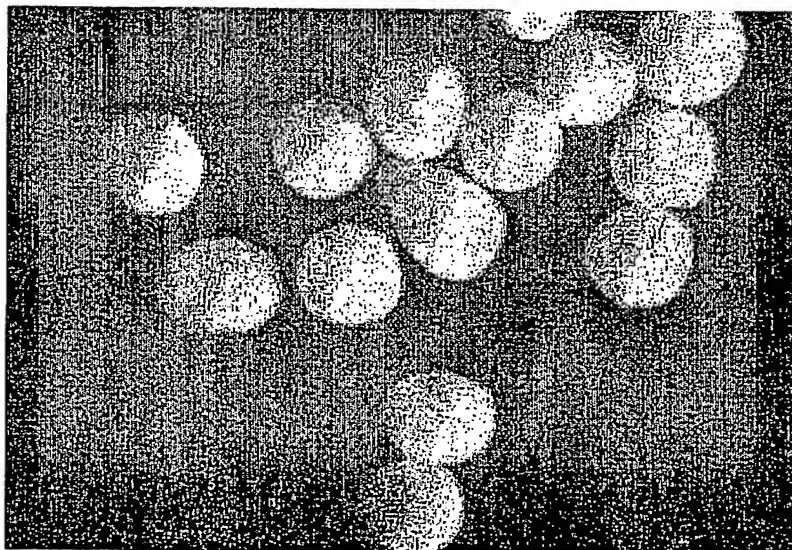
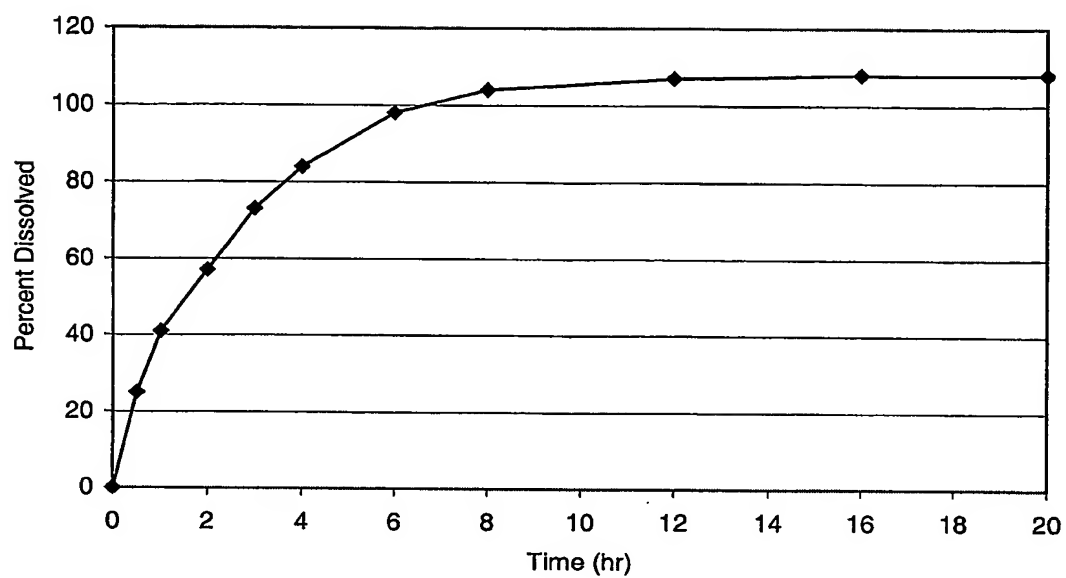


Figure 3(B)



**Figure 4**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/13099

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 9/16, 9/22, 9/32, 9/34, 9/36, 9/38, 9/54

US CL :424/458, 464, 468, 474, 477, 480, 481, 482, 489

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/458, 464, 468, 474, 477, 480, 481, 482, 489

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,940,588 A (SPARKS et al) 10 July 1990, see figures 1 and 2, example 21, claims 1-7.	1-38
A	US 5,455,047 A (BEQUETTE et al) 03 October 1995, see figures 9-11, column 4, line 24 through column 6.	1-38

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"G" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

29 JUNE 2003

Date of mailing of the international search report

26 AUG 2003

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/13099

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

WEST- search terms: irregular shape particle or matrix tablet, Wadell sphericity, roundness value, sustained release or controlled release or delayed release matrix particle, non spherical matrix particle